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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Mario Clerici

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EXAMINER

BAUSCH, SARAE L

ART UNIT

PAPER NUMBER

1634

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/516,421	Applicant(s) CLERICI ET AL.	
	Examiner SARAE BAUSCH	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-20 is/are pending in the application.
- 4a) Of the above claim(s) 5-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3 and 4 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 November 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Currently, claims 1, 3-20 are pending in the instant application. Claim 2 has been canceled. Claim 1 has been amended while claims 5-20 have been withdrawn. This action is written in response to applicant's correspondence submitted 07/15/2008. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final.**

2. The amendment to the specification mailed 07/15/2008 has been entered.

Withdrawn Rejections

3. The rejections of claims 1, 3-4, under 35 U.S.C. 112, second paragraph, made in section 9, of the previous office action mailed 01/17/2008, is withdrawn in view of the amendment to the claims.

4. The rejections of claims 1 under 35 U.S.C. 102(b), made in section 11, of the previous office action mailed 01/17/2008, is withdrawn in view of the amendment to the claims.

5. The rejections of claims 1, 3, under 35 U.S.C. 102(b), made in section 12, of the previous office action mailed 01/17/2008, is withdrawn in view of the amendment to the claims.

Drawings

6. The drawings are objected to because the specification does not describe what the lanes in figure 2 represent. Furthermore, the specification on page 9 refers to the alleles of figure 2 however figure 2 demonstrates a gel. It is unclear if the specification on page 9 refers to the alleles in the figure or what is encompassed in the lanes of the gene which is not described. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Response to Arguments

7. The response traverses the objection on page 7-8 of the remarks mailed 07/15/2008. The response asserts that each lane represents a different sample and the specific identity of the sample is not relevant as the invention is based on population analysis not particular

characteristics of any single sample and the polymorphism detected in each group is clearly indicated by the figure legend. This response has been thoroughly reviewed but not found persuasive. The figure describes genotyping for six different samples however its unclear what each gel represents other than the allele, for example are the six different samples each gel or each sample within each of the gels. Applicant assert that each lane represents a different sample, however the specification on page 13 states that there are six different samples and each gel only has five lanes, thus its unclear if there are only five samples analyzed or six samples and if there six samples are analyzed its unclear where the six sample is presented on the gel since there are only five lanes. Additionally, its unclear from the description what each of the lanes represents, for example in figure 2A, there are five lanes two of five have different sizes based on the description its unclear if this represent that only two samples had the GCC/GCC allele. There is an inconsistency between the description of the figure and the figure itself (see pg. 8 and figure 2).

Information Disclosure Statement

8. It is noted that although the IDS filed on 11/29/2004 failed to comply with 37 CFR 1.98(a)(2) in that some non-patent literature publications were not provided, however as stated in the previous office action, the copies were available and places in the file and the IDS was fully considered. Applicant was reminded that any additionally IDS must include a copy of each non-patent literature publication.

Maintained Rejections

Claim Rejections - 35 USC § 112- Enablement

9. Claims 1 and 3-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was previously presented in section 01/17/2008 and has been rewritten to address the amendment to the claims and specification.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims

The claims are drawn to a method for the determining the existence of or predisposition to diagnosis of an individual's predisposition to Alzheimer's disease by determining the allelic

variant of G to A at -1082 of IL-10 in a subject animal. The claims are limited to additionally analyzing to determine the presence of -174C allele in IL-6 and ApoE4 carrier status. The claims are further limited to additionally analyzing to determine the presence of -1082A allele for IL-1.

The nature of the claims requires knowledge of a correlation between detection of the presence of a -1082A allele of IL-10, -174C allele of IL-6, -1082A allele of IL-1, the status of ApoE4 carrier and diagnosis and predisposition to Alzheimer's disease (AD).

The invention is in a class of inventions which the CAFC has characterized as "the unpredictably arts such as chemistry and biology" (Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Guidance in the Specification and Working Examples

The specification teaches the present invention is related to a process of whether IL-10 and IL-6 SNPs were related with the development of AD (pg 3, 2nd last para.). The specification teaches that AD is a clinical syndrome characterized by complex and heterogeneous pathogenic mechanisms (see pg. 1, last para). The specification teaches that the allele e4 of ApoE significantly increases the risk of AD but it is neither necessary nor sufficient for the development of the disease (See pg. 2, 1st paragraph).

The specification asserts that the combination of IL-10 and IL-6 has been found to be more strongly predictive of predisposition to Alzheimer's disease (see pg. 9, 2nd para.). The specification further teaches that ApoE has been associated with sporadic and non-sporadic Alzheimer's and hence a further aspect is the polymorphic allele of IL-10, IL-6, and Apo-E (see

pg. 9, 3rd para). The specification further asserts the presence or absence of additional allelic variations of cytokines, specifically IL-10, IL-6, Apo-E and IL-1 (see pg. 9, 5th para.)

The specification demonstrates a working example (example 1) of 47 AD patients and 25 non-demented subjects (see pg. 13, last para). The specification demonstrated whole blood samples were taken and genotyped for IL-10 (see pg. 14). The specification demonstrates genotyping for the promoter region of IL-10 and performing statistical analysis (See pg. 15). The specification teaches that different IL-10 genotypes among AD patients was significantly skewed as shown in table II. However table II demonstration the relation to age of AD onset and table I demonstrates the frequency of different genotypes of AD patients to healthy controls (table I, table II and pg. 16, 1st full para). The specification asserts that the frequency of different genotypes among AD patients was statistically different from health controls and gives a p value of .007, however the specification does not provide any guidance with what the p value represents, its unclear if its the comparison of all alleles of AD to healthy control or specific individual allele of AD to healthy control (see pg. 4, last para). The specification asserts that the presence of the ATA/ATA and GGC/ATA genotypes were associated with earlier age at disease onset with a p value of .042 demonstrated in table II and the inverse correlation was detected for low IL-10 producing genotypes, table III.

The specification demonstrates a working example of 65 AD patients and 65 health controls (See pg. 22, example 2). The specification teaches obtaining blood samples from the individuals and genotyping the samples for IL-10 and IL-6 as well as ApoE genotype (See pg. 23). The specification teaches that the genotype and allele frequencies of the biallelic polymorphism at position -1082 is reported in table V (see pg. 24). The specification asserts that

AD patients who a significantly higher frequency of -1082A which skews the genotype distribution in AD compared to healthy controls (see pg. 24). Table V demonstrates that the A allele is statistically significant in the population of AD patients analyzed however it unclear how the distribution of the allele and p values were determined. According to table V, there were 90 AD patients with the A allele and 36 patients with the G allele, which teaches that 126 AD patients, however the specification teaches that only 65 patients were analyzed. (see pg. 25 and pg. 23). The specification asserts that table VI shows the distribution of IL-6 with AD and healthy control patients. According to table VI, the allele is statistically significant however table VI demonstrates a total of 118 AD patients, 50 with C allele and 68 with G allele but the specification teaches that only 65 patients were analyzed (see pg. 26 and pg. 23). Table VII of the specification demonstrates the IL-10 and IL-6 allele risk for AD however the A allele of IL-10 and the C allele of IL-6 has a p value greater than .05 (see pg. 27).

The specification does not teach the analysis of IL-1 or ApoE4 carrier in AD patients.

The following is unclear from the teaching in the specification. The data that presents the potential correlation between -1082A IL-10 alone and -174C IL-6 alone does not correspond to the patient population that was tested. It is unclear if there were more patients tested in tables V and table VI or if tables V and VI represented something else. The specification does not teach predictably associating the -1082A of IL-10, -174C of IL-6, ApoE4 carrier or -1082A IL-1, alone or in combination with diagnosis or predisposition to AD in any human.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does teaches is replete with evidence that association of -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 is unpredictable as larger genotyping studies of different ethnicities of AD patients did not find a predictable correlation between -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 alone or in combination with diagnosis or predisposition to AD in any human or non-human animal.

Furthermore, the post filing art is replete with evidence that association of -1082A of IL-10, -174C of Il-6, ApoE4 carrier or -1082A IL-1 is unpredictable. The prior art analyzes several different populations and larger sample sizes and found that each of the alleles -1082A of IL-10, -174C of Il-6, or -1082A IL-1 is not predictably correlative to diagnosis or predisposition to AD.

The post filing art teaches that -1082A is not associated with AD in different populations. For example, Bagnoli et al. (Neuroscience Letters (207 418:262-265) teaches that there have been conflicting results of IL-10 polymorphisms and their association with AD (See abstract). Bagnoli et al. teach that three studies in Italian and Chinese populations demonstrate that -1082A allele of Il-10 is significantly over represented in AD patients however there are other studies that have not been able to replicate these results and that the role of IL-10 gene in AD may be limited to certain populations (See pg. 262, last para.). Bagnoli et al. analyzed -1082A of 222 AD patients and 179 normal controls (see pg. 263, 1st column, 1st para.). Bagnoli et al. teach

many authors have investigated the role of -1082A allele as genetic risk factor for AD with conflicting results. Bagnoli et al. teach a study of 132 AD patients from northern Italy found the -1082A allele was increased in AD patients, in contrast a study of 406 German AD patients and 215 Italian AD patients did not replicate these findings, and finally another paper of an American population found no statistical significance in the case-control groups (see pg. 264, 1st column, last para.) Bagnoli et al. teach that no overexpression of the -1082A allele or distribution was found in AD patients, which confirm two Italian studies and a Chinese case-control study (See pg. 264, 1st column, last para.) Therefore, Bagnoli et al. demonstrate the unpredictability of association -1082A allele with AD in a small population study, such as that taught in the instant specification.

Additional post filing art teaches the unpredictability of association -174C allele of IL-6 with AD. Capurso et al. (Exp. Gerontology, 2004, vol. 39, pp. 1567-1573) teach a genotyping study of AD patients in northern and southern Europe (see abstract). Capurso et al. teach multiple studies have been conducted to determine the association of -174G/C allele with AD (see table 1). Capurso et al. teach that the association between IL6 -174 G/C promoter polymorphism and increased risk of AD has been evaluated in four ethnic groups with contrasting findings (See pg. 1568, 1st column, 1st para.) Capurso et al. teach analysis of 388 subjects from southern Italy with 168 AD patients (See pg. 1568, 2nd column, last para.). Capurso et al. teach no evidence of an association of IL-6 -174 G/C promoter polymorphism with AD. Capurso et al. teach a study with larger sample size did not show an association with IL-6 -174 G/C promoter polymorphism and risk for AD (see pg. 1571, 2nd column, last para). Capurso et al. teaches the explanation of the conflicting results is unclear but that perhaps there

is linkage disequilibrium with another biological relevant locus on chromosome 7 or the polymorphism is due to non-random association with a functional mutation on the gene (see pg. 1572, 1st column, 1st full para) Capurso et al. teaches that a large meta-analysis of genetic association studies with common diseases indicate that only a third to a half of all associations ultimately prove to be significant, emphasizing the importance of larger samples (See pg. 1572, 1st column, 1st full para).

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to

complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph).

Additional post filing art reveals that most gene association studies are typically wrong.

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands) might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of 5×10^{-8} , however arguments from Bayesian perspective suggest that 5×10^{-5}

should be sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate with the following alleles -1082A of IL-10, -174C of IL-6, ApoE4 carrier or -1082A IL-1, alone or in combination with AD, as the specification does not teach a large sample size, analyze different ethnic groups or provide confidence levels greater than 95% for the following alleles -1082A of IL-10, -174C of IL-6, ApoE4 carrier or -1082A IL-1, alone or in combination. The specification only teaches a subject population of 65 AD patients with statistically significant data for the analysis of an association between -1082A IL-10 and AD patients however the number of patients in the table (Table V) is not consistent with the sample population and further the post filing art demonstrates that in a larger sample size in different ethnicities was demonstrated not to be predictably correlative to AD.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to the association the following alleles -1082A of IL-10, -174C of IL-6, ApoE4 carrier or -1082A IL-1, alone or in combination with AD the quantity of experimentation in this area is extremely large. The skilled

artisan would have to perform an extremely large study and include different populations and familial studies for each of the polymorphisms -1082A of IL-10, -174C of IL-6, ApoE4 carrier or -1082A IL-1, alone or in combination with AD to determine if in fact there was either an association between the polymorphism an individuals and AD. The results of such a study are unpredictable as evidence by the post filing art (which reflects the current state of the art) and the teachings in the specification. In the instant case, it would be unpredictable as to whether or not the following alleles -1082A of IL-10, -174C of IL-6, ApoE4 carrier or -1082A IL-1, alone or in combination would be responsible for determining the predisposition or diagnosis to AD in any human. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to AD. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Response to Arguments

10. The response traverses the rejection on pages 9-11 of the remarks mailed 07/15/2008. The response asserts that there is literature that confirms the study upon which the present application is based and cites Combarros et al, Ma et al, and Infante et al. However, Combarros et al. teaches that only heterozygosity of IL-10 at -1082A allele was associated with a small increase of AD risk (see pg. 864, 2nd column, last para and table 1). Additionally, Combarros et al. teaches that their study does not allow for rigorous analysis of gender specific differences in AD risk association and additional studies using different sets of patients and controls are

required to confirm the effect, thus Combarros et al. does not confirm what is present in the specification as Combarros et al. teaches that there is only a small effect seen with only the heterozygous -1082 A allele and teaches that more studies are necessary. Ma et al. teach that genotypic distribution in the AD group did not differ significantly from the control group for the IL-10 -1082 polymorphism (see pg. 1007, 2nd para, 1st full para). Mat et al. teach that there are ethnic differences between populations that may account for the different associations with the disease (see pg. 1009, 1st column, last para). Ma et al. does not teach a predicative association of any allele of -1082 with risk of AD (See table 2). Thus Ma does not provide evidence that the study upon which the instant invention is based is predictive and infact teaches the unpredictability of association the -1082 allele with AD in different ethnic populations (see pg. 1009, 1st column, last para and pg. 1005, 2nd column, last para). Infante et al. teach a study of Caucasian subjects and teach that C/C genotype of IL-6 is related to decrease risk of AD and the A/A genotype of -1082 of IL-10 was not associated with AD (see pg. 1135, 2nd column, 1st full para). Infante et al. teach the interaction effect of both polymorphisms did have an effect on lower risk of developing AD. Thus, Infante et al. does not demonstrate the finding in the specification, as Infante et al. demonstrate that homozygous A at position -1082 of IL-10 along with homozygous C at position -174 of IL-6 is associated only with a decreased risk but -1082 alone is not predictive. It is noted that the claims are drawn to any risk, thus the claims encompass both an increase and decreased risk and claim 1 is drawn to both homozygous and heterozygous A of -1082 of IL-10 in any population. Thus neither Combarros, Ma, or Infante provide evidence that the claimed invention of any risk in any population of human, having either a homozygous or heterozygous -1082 of IL-10 is enable and in fact each of the reference

provide further evidence of the unpredictability of associating the polymorphism with Alzheimer's disease.

The response asserts that the claims are to a method that is useful or predictive in determining a predisposition or as a diagnostic rather than an absolute diagnosis and as such the method is fully enabled. This response has been thoroughly reviewed but not found persuasive. The claims are drawn to a diagnostic method and/or screening for predisposition of AD and not to a method of screening for a polymorphism, thus the claims require the knowledge of a correlation between detection of a -1082A allele and predisposition to AD. Thus, the claims require a predicative association between -1082A allele and AD and the evidence in the art demonstrates the unpredictability of associating -1082A allele in IL-10 in any population with any risk of AD.

The response on page 10 addresses points addressed by the examiner, specifically, the response addresses the incorrect table references in the specification and states that 6 patients could not be reliably typed due to insufficient number of cells. However, it is noted, as stated in the paragraph above even with the correction of the table references in specification, the claims require the correlation between detection of -1082 A of IL-10 and predisposition of AD. As evidence in the art, the association of -1082A of IL-10 with increase or decrease risk of AD in any ethnic population is unpredictable thus claimed invention is not enabled.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112- Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 3-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is newly presented, necessitated by the amendment to the claims.

Claim 1 recites the limitation "said subject animal" in 4. There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites "human subject" in line 3 of the claim and therefore the claim is indefinite as it is not clear that subject animal is referring to human subject or if subject animal is an additional subject analyzed in the claim. It is suggested to amend the claim to recite either said subject or said human subject.

Conclusion

13. No claims are allowable.
14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E BAUSCH whose telephone number is (571)272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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